EXHIBIT D

EPA/EPO/OEB
D-80298 München
+49 89 2399-0
TX 523 656 epmu d
FAX +49 89 2399-4465

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Burkert, Frank
Bayer AG,
Konzernbereich RP
Patente und Lizenzen
51368 Leverkusen
ALLEMAGNE

Telephone Numbers:

Primary Examiner (substantive examination) +49 89 2399-7519

Formalities Officer / Assistant (Formalities and other matters) +49 89 2399-8131

Application No.	Ref.	Date
96 114 439.1-2113	MSB007232-EP	06.12.2000
Applicant: Bayer Corporation		

Communication pursuant to Article 96(2) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(1) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 78(2) and 83(2) and (4) EPC.

Amendments to the description, claims and drawings are to be filed where appropriate within the said period in three copies on separate sheets (Rule 36(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Article 96(3) EPC).

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LUETHE H
Primary Examiner
for the Examining Division

EXR1 001206 EXR2 04M coded

Enclosure(s): 4 page/s reasons (Form 2906)

Registered Letter
EPO Form 2001 05 00CSX

PI22115, 01.12.2000

Bescheid/Protokoll (Anlage)		Communication/Minutes (Annex)		Notification/Procès-verbal (Annexe)	
Datum Date Date	**CODINGDATE**	Blatt Sheet Feuille	1	Anmelde-Nr.: Application No.: Demande n°:	96 114 439.1

The examination is being carried out on the **following application documents:**

Text for the Contracting States:
AT BE CH LI DE DK ES FI FR GB GR IE IT LU MC NL PT SE

Description, pages:

1-20 as originally filed

Claims, No.:

1-24 as originally filed

Drawings, sheets:

1/1 as originally filed

1. The following documents (D1 and D2) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

   D1: US-A-4 540 573 (NEURATH ALEXANDER R ET AL) 10 September 1985
   D2: US-A-4 396 608 (TENOLD ROBERT A) 2 August 1983

2. The application does not meet the requirements of Article 84 EPC, because claim 1 is not clear.

2.1. According to the present wording of claim 1 "a solution of antibodies which **may** have virus activity" (emphasis by the examining division) its scope embraces solutions which **do not** have virus activity.
For the latter solutions, however, step a) of claim 1, i.e. the step "to substantially reduce any virus activity" is superfluous and, hence, step b), i.e. "incubating the solution ... such that the anticompliment activity of the solution is reduced" as well, since the anticompliment activity results from step a) (cf. last line of a)).
This inconsistency leads to an ambiguity about the scope of the claim, thus rendering it unclear; accordingly, the claim requires amendment to remove this

defect (Article 84 EPC).

2.2. Claim 1 does not meet the requirements of Article 84 EPC in that the matter for which protection is sought is not defined. The claims attempt to define the subject-matter in terms of the result to be achieved (cf. a) "under conditions sufficient ... activity" and b) "under conditions of ... such that ... reduced"). Such a definition is only allowable under the conditions elaborated in the Guidelines C-III, 4.7. In this instance, however, such a formulation is not allowable because it seems possible to define the subject-matter in more concrete terms, viz. in terms of how the effect is to be achieved (cf. claims 2, 7-10, 20; tables 6 and 7).

2.3. The objection under point 2.2 can also be worded as follows:
It is clear from the description (cf. page 5, 4th paragraph to page 10, first paragraph) that not any method as represented by steps a) and b) of claim 1 solves the problem posed, that is to reduce both the virus activity and anticomplement activity but only those which are limited by certain process parameters, such as processing time, pH, temperature, ionic strength etc. Hence, presently claim 1 covers subject-matter, i.e. compositions, which do not form a solution to the problem to be solved and, thus, it would appear that claim 1 does not contain all features essential to the invention as required by Article 84 taken in combination with Rules 29(1) and (3) EPC.

To overcome this objection the claim should be drafted in a such a way that it contains all the technical features essential to the invention.

2.4. The term 'about' used in claims 2-8, 10, 11, 15, 16, 20-24 is vague and indefinite and, as such renders the claim unclear (Article 84 EPC; Guidelines C-III, 4.5a). Especially when used to define the terminal points of ranges (see present claims 8, 15, 16, 20, 21, 23) it does not allow for a meaningful comparison with numerical data of prior art documents anymore.
This defect requires amendment of the claim in order to render the features concerned unequivocal.

3. In so far as what can be understood from the Claims:

The present application does not meet the requirements of Article 52(1) EPC, because the subject-matter of claims 1-24 does not involve an inventive step in the sense of Article 56 EPC.

3.1. The details of both steps a) and b) of method claim 1 are known as such.
Step a): Document D1 (for citations see the European Search Report).
Step b): Document D2 (for citations see the European Search Report).

3.2. The applicant's has acknowledged (cf. page 17, second paragraph) that according to D2 the anticomplementary activity, 'ACA', does not derive from a viral activation step but rather from other sources (cf. D2: col. 1, lines 23-29).
It is further clear from D2 that its method for treating immun serum globulin is not restricted to any or specially adapted to any discrete gamma globulin preparation or source of the anticomplementary activity:
"The **usual** intramuscular gamma globulin preparations cannot safely be administered intravenously because such administration causes an unacceptably high incidence of reactions, especially in agammaglobulinemic recipients" (cf. col. 1, lines 16-19; emphasis by the examining division). "Several approaches have been taken to the problem of rendering gamma globulin safe for intravenous administration. All of these are dependent on eliminating its anticomplement activity" (cf. col. 1, line 35-38) and "The gamma globulin of this invention is substantially free from anticomplement activity, both immediate and latent" (cf. col. 8, lines 8-10).

3.3. Hence, the person skilled in the art starting from the process of D1 (anticipating step a) of present claim 1) would indeed, when confronted with the teachings of D2 (anticipating step b) of present claim 1), apply the method of D2 to arrive at the method of present claim 1.
Accordingly is the immun serum globulin preparation of present claim 21 not inventive.

3.4. The features of claims 2-20 and 22-24 are either known from the prior art documents or do not seem to represent features which, in combination with the features of any claim to which they refer, involve an inventive step.

Bescheid/Protokoll (Anlage)		Communication/Minutes (Annex)		Notification/Procès-verbal (Annexe)	
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4. If new claims are to be filed
At an appropriate stage in the procedure:
The description must be brought into conformity with the new claims to be filed; care should be taken during revision, especially of the introductory portion including any statements of problem or advantage, not to add subject-matter which extends beyond the content of the application as originally filed, Article 123(2) EPC; the latter applies also to amendments in general.

Amendments should be filed by way of replacement pages, avoiding unnecessary recasting of the description and account taken of the requirements of Rule 36(1) EPC. In particular, fair copies of the amendments should be filed in triplicate.

In order to expedite the procedure the letter of reply should indicate the locations in the application as originally filed of the passages forming a basis for the amendments (cf. Guidelines E II, 1. and 2.)

H. LÜTHE

Dr. Frank Burkert
European Patent Attorney

Bayer AG
Konzernbereich RP
Patente und Lizenzen
51368 Leverkusen
Telefon: 0214-30-61455

EPO - Munich
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European Patent Office
Erhardtstraße 27
80298 München

pAL

European Patent Application No. 96114439.1-2113

In response to the Summons to Attend Oral Proceedings Pursuant to Rule 71 (1) EPC dated September 21, 2001, and in preparation of the Oral Proceedings. Applicant submits this written submission and amendment.

Applicant herewith files a new set of twenty (20) claims for further prosecution.

Claim 1 has been amended to clarify the method steps by reciting the intended purpose of the method in the preamble, by adding specific references to the antibody solutions prepared as a result of each step in the method, and by adding the step of removing trialkylphosphate and detergent prior to step c) incubation. Support is found at page 7, lines 10-12 (removing trialkylphosphate and detergent before step c)).

Claims 2-6 have been amended to conform to the newly added specific references to the antibody solutions produced at each step in claim 1. Original claims 7-10 were cancelled in Applicant's amendment of April 9, 2001.

The new claims show original claims 11-24 renumbered to reflect the cancellation of claims 7-10. Renumbered claims 7-20 have been amended as needed to reflect the specific references to the antibody solutions produced at each step in claim 1. Renumbered claim 8 has been amended to specify that tonicity is adjusted between steps b) and c), which is supported by the specification at page 8, line 20 to page 9, line 6. The claim amendments are made solely for the sake of clarity.

In Section 2 of the Summons, the Examining Division stated that the objections outlined in the communication dated December 6, 2000 under point 2 (with respect to step a) of claim 1) and point 3 are maintained in full.

With regard to clarity of step a) in claim 1, the Examining Division stated that the requirements of Article 84 EPC were not met because the matter for which protection is sought is not defined as described in the Guidelines C-III, 4.7. The Examining Division argued that defining step a) using the results to be achieved (c.f. "under conditions sufficient to substantially reduce any viral activity") was impermissible because it seems possible to define the subject matter more concretely by how the effect is to be achieved. Applicant respectfully disagrees.

Guidelines C-III, 4.7 allows for claiming by the result to be achieved when specifying the conditions to achieve the result would unduly restrict the claim scope:

> However, they [claims reciting a result to be achieved] may be allowed if the invention cannot otherwise be defined more precisely without unduly restricting the scope of the claims and if the result is one which can be directly and positively verified by tests or procedures adequately specified in the description or known to the person skilled in the art and which do not require undue experimentation. (see T68/85, OJ 6/1987,228)

Here, such a broad range of conditions may be used to achieve the recited result of substantially reducing the viral activity that the invention would be unduly restricted if Applicant was required to list them all. For example, U.S. Patent 4,540,573, which is incorporated by reference into the present specification, discloses at column 7, lines 46-49 that the trialkylphosphate can be employed in any amount between about 0.01 mg/ml and about 100 mg/ml. Furthermore, the '573 patent also teaches that the amount of detergent employed "is not crucial" and may be from about 0.001% to about 10% (id. at col. 8, lines 35-37). The particular trialkylphosphate and detergent employed may be selected from a large group. See id. at col. 7, lines 29-44 (trialkylphosphates) and at col.7, line 61 to col. 8, line 11 (detergents). Treatment may occur at a broad range of temperatures between -5°C and 70°C, for any time beyond at least one hour (id. at col. 9, lines 11-16). Furthermore, the present specification teaches that step a) may occur at a wide range of pH depending upon the detergent employed (page 6, lines 11-13). This evidence shows that to restrict the scope of step a) to recite the terms under which viral activity is substantially reduced would unduly restrict the claim scope to conditions not reflective of the full scope of the invention.

Furthermore, one skilled in the art would know how, without undue experimentation, to verify substantial reduction of viral activity using standard viral titer measurements. At page 3, lines 19-20 of the specification, Applicant discusses that the claimed process "results in a substantial reduction (i.e. at least 4 logs) in the titer of lipid enveloped viruses".

The methodology to measure titer of lipid enveloped viruses are well known to those skilled in the art. For example, protocols are found in Bundesgesundheitsamt und Paul-Ehrlich-Institut Bundesamt für Sera und Impfstoffe, "Bekanntmachung über die Zulassung von Arzneimitteln. Arforderungen an Validierungsstudien zum Nachweis der Virussicherheit von Arzneimitteln aus menschlichem Blut oder Plasma", 20 December 1993/21 January 1994, Bundesanzeiger 4 May (1994) and CPMP Note for Guidance on Virus Validation Studies: The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses, CPMP/BWP/268/95 Final Version 2 (1996).

For these reasons, Applicant submits that step a) of claim 1 meets the preciseness requirement of Article 84 by reciting the result of substantial reduction in viral activity rather than attempting to delineate the many conditions that can be used to achieve that result.

With regard to inventive step (Article 56 EPC), the Examining Division stated that the cumulative steps of a) and b) (now c) do not form the basis of an inventive step because the person skilled in that art would, without inventive skill, combine the teachings of D1 and D2 to arrive at the method of claim 1. Applicant respectfully disagrees.

The present invention solves the problem of obtaining an antibody solution which is both low in anticomplement activity and has been subjected to viral inactivation. See the specification at page 3, lines 5 and 6.

D1 discloses a method of inactivating viruses in protein-containing compositions derived from blood without substantial protein denaturation wherein the composition is contacted for a sufficient period of time with a di- or trialkylphosphate to inactivate viruses present in the composition. The treatment of the composition can also be done in the presence of a wetting agent such as a detergent.

D2 discloses immune serum globulin solutions suitable for intravenous injection and methods for preparing such solutions. The method disclosed in D2 comprises the steps of adjusting the pH of an aqueous solution of an immune serum globulin to about 3.5 –5.0 by addition of a physiologically acceptable acid, reducing the ionic strength of the solution such that a 5% protein concentration has a nephelometric reading less than 15 NTU, while maintaining the pH, and adjusting the tonicity of the solution to a physiologically acceptable level by addition of an amino acid, carbohydrate or sugar alcohol.

D2 does not disclose step c) of claim 1 of incubating the virus inactivated antibody solution for a period of at least about ten days under the conditions set out in the claim.

Simply combining the steps of viral inactivation, as disclosed by D1, followed by formulation of the antibody solution, as disclosed by D2, does not provide the claimed methods and compositions. At page 2, lines 23-27 of the specification, Applicant reported that using a viral inactivation step like that in D1 and subsequently formulating according to D2 "results in a product with an acceptable viral inactivation but with unacceptably high levels of ACA [anticomplement activity]". The experiments leading to this conclusion are reported at page 10, line 5 – page 12, and Table 1 of the specification. The combination of D1 and D2, therefore, does not solve the problem of obtaining an antibody solution for intravenous injection that is both low in anticomplement activity and has been subjected to viral inactivation.

Applicant discovered surprisingly that treating an antibody solution with a trialkylphosphate and a detergent to inactivate any virus activity followed by incubating the antibody solution for at least about ten days under controlled conditions of pH, temperature, and ionic strength, solves the problem of providing an antibody solution that has been subjected to viral inactivation and has anticomplement activity at levels acceptable for intravenous injection. Neither D1 nor D2 suggest that incubation is needed after viral inactivation. The step of incubating the antibody solution surprisingly provides an antibody solution with the desired characteristics of low anticomplement activity and viral inactivation.

The method of claims 1-16 and the immune serum globulin preparation of claims 17-20, which are prepared by the method of claim 1, accordingly contain an inventive step and are in compliance with Article 56 EPC.

Furthermore, one skilled in the art would not look to D2 to solve the problem addressed by the present invention.

Applicant found that subjecting an antibody solution to a viral inactivation step involving a trialkylphosphate and a detergent surprisingly resulted in an increase in anticomplement activity. See the specification at page 11, Table 1. The problem addressed by the invention is this increase in anticomplement activity after viral inactivation. The Applicant found that, unlike the art, this new anticomplement activity was not related to antibody aggregation. See page 13, Table 4. In contrast, D2 teaches that anticomplement activity of an antibody solution can be controlled by conditions of ionic strength and pH "such that the monomer content of the immune serum globulin [i.e., antibody] is greater than about 90%". (Emphasis added) D2 at col. 4, lines 21-29. Also, Example 1 of D2 shows that measurements of monomer level are indicative of stability, and thus, of anticomplement activity. Thus, D2 teaches reducing anticomplement activity by reducing aggregation.

Yet Applicant found no increased aggregation in viral-inactivated solutions. Thus, there would be no suggestion to follow viral inactivation with the formulation of D2, because D2 teaches to reduce aggregation and

aggregation is not a problem. For this reason, one skilled in the art starting from the process of D1 would not expect to formulate antibodies according to

of D2 to solve the problem of high anticomplement activity. For this additional reason, it is submitted that the claims comply with Article 56 EPC.

It is kindly requested that any amendment to the specification be delayed until agreement regarding allowable claims has been reached. Allowance of the present claims is requested.

(Dr. Frank Burkert)
General Authorization No. 18552)
Enclosure

Enclosure: EP App. No. 96114439.1-2113
MSB 7232EP/2002-01-22

CLAIMS

1. A method for the preparation of an antibody solution having low viral activity and low anticomplement activity, the method comprising:

   a) contacting a first antibody solution with a trialkylphosphate and a detergent under conditions sufficient to substantially reduce viral activity present in the first antibody solution to produce a second antibody solution;

   b) removing trialkylphosphate and detergent from the second antibody solution to produce a third antibody solution, and

   c) incubating the third antibody solution for a period of at least about ten days at a pH maintained between about 3.5 and about 5.0, a temperature within a range of about 2°C to about 50°C, and at an ionic strength of less than about 0.001 to produce the antibody solution having low viral activity and low anticomplement activity.

2. The method of claim 1, wherein the anticomplement activity of the antibody solution is less than about 60 CH_{50} units/ml.

3. The method of claim 1, wherein the antibody solution comprises about 5% wt./wt. antibody and has an anticomplement activity of less than about 45 CH_{50} units/ml.

4. The method of claim 3, wherein the antibody solution comprises about 5%wt./wt. antibody and the anticomplement activity is less than about 30 CH_{50} units/ml.

5. The method of claim 1, wherein the antibody solution comprises about 10% wt./wt. antibody and has an anticomplement activity of less than about 60 CH_{50} units/ml.

6. The method of claim 5, wherein the antibody solution comprises about 10% wt./wt. antibody and has an anticomplement activity of less than about 45 CH_{50} units/ml.

7. The method of any of claims 1 to 6, wherein at least about 99% of the antibodies in the antibody solution are monomeric.

8. The method of claim 1, wherein between steps b) and c), tonicity of the third antibody solution is adjusted to a physiologic value under such conditions that the ionic strength of the third antibody solution is not appreciably altered.

9. The method of claim 8, wherein the tonicity of the solution is adjusted by adding a carbohydrate to the third antibody solution.

10. The method of claim 9, wherein the carbohydrate is maltose.

11. The method of claim 8, wherein the tonicity of the third antibody solution is adjusted to a range of about 230 to about 490 mosmol/kg solvent.

12. The method of claim 11, wherein the tonicity of the third antibody solution is adjusted to a range of about 274 to about 309 mosmol/kg solvent.

13. The method of claim 8, wherein the tonicity of the third antibody solution is adjusted by adding an amino acid to the third antibody solution.

14. The method of claim 13, wherein the amino acid is glycine.

15. The method of any of claims 1 to 14, wherein the trialkylphosphate is tri-n-butylphosphate and the detergent is selected from polysorbate 80 and sodium cholate.

16. The method of any of claims 1 to 15, wherein the first antibody solution is contacted with trialkylphosphate and detergent at a pH between about 3.5 and 6.0.

17. An intravenously injectable immune serum globulin preparation produced by the method of claim 1 and substantially free of lipid enveloped viruses, wherein the preparation has an ionic strength of less than about 0.001, a pH between about 3.5 and 5.0, antibody concentration of about 5% wt./wt. and a maltose concentration of about 10% wt./wt.

18. The preparation of claim 17, wherein the pH is about 4.25.

19. An intravenously injectable immune serum globulin preparation produced by the method of claim 1 and substantially free of lipid enveloped viruses, wherein the preparation has an ionic strength of less than about 0.001, a pH between about 3.5 and about 5.0, an antibody concentration of about 10% wt./wt. and a glycine concentration of about 0.2M.

20. The preparation of claim 19, wherein the pH is about 4.25.